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Gene Therapy-A Novel Approach in Genetics

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Abstract: ***Gene therapy is the therapeutic delivery of nucleic acid polymers into a patient's cells as a drug to treat disease. Gene therapy could be a way to fix a genetic problem at its source. The polymers are either expressed as proteins, interfere with protein expression, or possibly correct genetic mutations. The most common form uses DNA that encodes a functional, therapeutic gene to replace a mutated gene. The polymer molecule is packaged within a "vector", which carries the molecule inside cells. This therapy offers a promising new approach to treating a range of diseases including various forms of cancer, inherited disease and certain viral infections. However, further studies are still required to ensure the safety and effectiveness of these techniques. Currently, the therapy is only used to treat diseases where other therapies are already known to be ineffective. It is a novel form of drug delivery that enlists the synthetic machinery of the patient's cell to produce a therapeutic agent. It involves the efficient introduction of functional gene into the appropriate cells of the patient in order to produce sufficient amount of protein encoded by transferred gene (transgene) so as to precisely and permanently correct the disorder.***

Keywords: Gene therapy, DNA, Mutated gene, Vector, Transgene

1. Introduction

There are three main strategies in gene therapy.
1) Gene addition.
2) Removal of a harmful gene by antisense nucleotide or ribozyme.
3) Control of gene expression.

Gene therapy has various potential advantages over drug therapy like:-
1) Functional gene can replace a dysfunctional gene or deficient gene.
2) Transgene can result into continuous production of a therapeutic protein that normally has a short half life.
3) Gene therapy can be focused to a specific cell type to avoid potentially toxic systemic effects.
4) Gene therapy can improve patient's compliance and decrease cost of therapy on long term bases.

There are two basic types of gene therapy: germline therapy and somatic gene therapy.

2. Germline Therapy

This therapy involves the modification of the genes inside germ cells (sperm or ova). During reproduction, these gamete cells fuse to form a zygote, which would divide and pass on the modified gene into all other cells of the body during the development of offspring. In this way, the therapy alters the genome of future generations to come.Although theoretically this could counteract hereditary disease, jurisdictions in various countries such as Switzerland, Australia and Germany prohibit the use of germline therapy due to fears over unknown risks and long-term effects in future generations. In addition, the therapy is very costly.

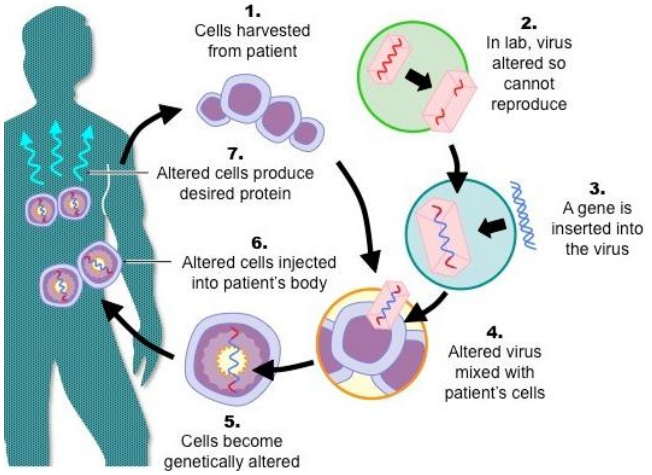

Figure 1: showing process of insertion of correct gene in human cell .

Somatic gene therapy

Unlike germline therapy, somatic gene therapy only involves the insertion of therapeutic DNA into body cells and not the germ cells or gametes. This means any effects of the therapy are confined to the individual being treated and are not inherited by future offspring.

The field of somatic gene therapy is surrounded by fewer ethical issues compared with germline gene therapy, although the therapeutic approach is also still in the early stages of design and prone to obstacles. The delivery of DNA into cells can be accomplished by multiple methods. The two major classes are recombinant viruses (sometimes called biological nanoparticles or viral vectors) and naked DNA or DNA complexes (non-viral methods).

Viruses

In order to replicate, viruses introduce their genetic material into the host cell, tricking the host's cellular machinery into using it as blueprints for viral proteins. Scientists exploit this by substituting a virus's genetic material with therapeutic DNA. (The term 'DNA' may be an oversimplification, as some viruses contain RNA, and gene therapy could take this form as well.) A number of viruses have been used for human gene therapy, including retrovirus, adenovirus, lentivirus, herpes-simplex, vaccinia and adeno-associated

virus.[2]Like the genetic material (DNA or RNA) in viruses, therapeutic DNA can be designed to simply serve as a temporary blueprint that is degraded naturally or (at least theoretically) to enter the host's genome, becoming a permanent part of the host's DNA in infected cells.

Non-viral

Non-viral methods present certain advantages over viral methods, such as large scale production and low host immunogenicity. However, non-viral methods initially produced lower levels of transfection and gene expression, and thus lower therapeutic efficacy. Later technology remedied this deficiency.

Methods for non-viral gene therapy include the injection of naked DNA, electroporation, the gene gun, sonoporation, magnetofection, the use of oligonucleotides, lipoplexes, dendrimers, and inorganic nanoparticles.

Gene therapy was conceptualized in 1972, by authors who urged caution before commencing human gene therapy studies. The first gene therapy experiment approved by the US Food and Drug Administration (FDA) occurred in 1990, when Ashanti DeSilva was treated for ADA-SCID.[1] By January 2014, some 2, 000 clinical trials had been conducted or approved.[2]

Early clinical failures led to dismissals of gene therapy. Clinical successes since 2006 regained researchers' attention, although as of 2014, it was still largely an experimental technique.[3] These include treatment of retinal disease Leber's congenital amaurosis, [4, 5, 6] X-linked SCID, [7] ADA-SCID, [8, 9] adrenoleukodystrophy, [10] chronic lymphocytic leukemia(CLL), [11] acute lymphocytic leukemia (ALL), [12] multiple myeloma, [13] haemophilia[9] and Parkinson's disease.[14] Between 2013 and April 2014, US companies invested over $600 million in the field.[15]

The first commercial gene therapy, Gendicine, was approved in China in 2003 for the treatment of certain cancers.[16]

Disadvantages of Gene Therapy No therapy, established or experimental, is without some associated risks. As human gene therapy is still a relatively new procedure, there are still many risks associated with it. Scientists do not yet understand all of the risks and there has not been enough time to complete detailed studies on how gene therapy works and the problems that it poses. Safety will appropriately remain an important consideration as the field of gene therapy evolves.

Some of the problems of gene therapy include:

- Short-lived nature of gene therapy: Before gene therapy can become a permanent cure for any condition, the therapeutic DNA introduced into target cells must remain functional and cells containing the therapeutic DNA must be long-lived and stable. Problems with integrating therapeutic DNA into the genome and the rapidly dividing nature of many cells prevent gene therapy from achieving any long-term benefits. Patients will have to undergo multiple rounds of gene therapy. Moreover, the new gene fails to express itself or the virus does not produce the desired response.
- Immune response: Anytime a foreign object is introduced into human tissues, the immune system has evolved to attack the invader. The risk of stimulating the immune system in a way that reduces gene therapy effectiveness is always a possibility. Furthermore, the immune system's enhanced response to invaders makes it difficult for gene therapy to be repeated in patient.[18]
- Problem with viral vectors: Viruses, while the carrier of choice in most gene therapy studies, present a variety of potential problems to the patients- toxicity, immune and inflammatory response and gene control and targeting issues. In addition, there is always the fear that viral vector, once inside the patient, may recover its ability to cause disease. • Multigenic disorders: Conditions or disorders that arise from mutation in a single gene are best candidates for gene therapy. Unfortunately, some of the most commonly occurring disorders, such as heart disease, high blood pressure, Alzheimer's disease, arthritis and diabetes, are caused by the combined effects of variations in many genes. Multigenic or multifactorial disorders would be especially difficult to treat effectively using gene therapy.[17]
- Insertional mutagenesis: The main problem that geneticists are encountering is the virus may target the wrong cells. If the DNA is integrated in the wrong place in the genome, [19] for example in a tumor suppressor gene, it could induce a tumor. This has occurred in clinical trials for X-linked SCID patients in which hematopoietic stem cells were transduced with a corrective transgene using a retrovirus, and this led to the development of T cell leukemia in 3 of 20 patients.
- Ethical and Social Consideration

Gene therapy is a powerful new technology that might have unforeseen risks, scientists first develop a proposed experiments i.e. protocol, that incorporates strict guidelines. After the approval from FDA, the organization continues to monitor the experiment. In the course of a clinical trial, researchers are required to report any harmful side effects. Critics and proponents all agree that risks of gene therapy must not be substantially larger than the potential benefit. Gene therapy poses ethical considerations for people to consider.[20]

Some of the ethical considerations for gene therapy include:

- Deciding what is normal and what is a disability;
- Deciding whether disabilities are diseases and whether they should be cured;
- Deciding whether searching for a cure demeans the live of people who have disabilities; • Deciding whether somatic gene therapy is more or less ethical than germ line gene therapy Initial experiments using gene therapy have been conducted primarily in patients for whom all other treatments have failed, so that the risks are small. Many people feel that because gene therapies use altered genes and potentially dangerous viruses, those treatments should be tested more extensively.

3. Conclusion

Most scientists believe the potential for gene therapy is the most exciting application of DNA science, yet undertaken.

How widely this therapy will be applied, depends on the simplification of procedure. Genes may ultimately be used as medicine and given as simple intravenous injection of gene transfer vehicle that will seek our target cells for stable, site-specific chromosomal integration and subsequent gene expression. And now that a draft of the human genome map is complete, research is focusing on the function of each gene and the role of the faulty gene play in disease. Gene therapy will ultimately play Copernican part and will change our lives forever.

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